



Artificial Intelligence in Herbal Medicine Development for Knee Osteoarthritis: Current Advances, Challenges and Future Perspectives

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Account Information	ABSTRACT
<i>Original Review article</i> Acceptance: Aug 2026 Published: September 2026 Volume 1 • Issue 1 • 2026 Keywords: <i>Knee osteoarthritis; Artificial intelligence; Herbal medicine; Network pharmacology; Chondroprotection; Matrix metalloproteinases; Molecular docking.</i>	Knee osteoarthritis affects over 360 million of individuals worldwide, causing articular cartilage degradation, subchondral bone transformation and chronic low-grade synovial inflammation. Current clinical management depend on primarily on oral acetaminophen and nonsteroidal anti-inflammatory drugs. These agents relieve joint discomfort for the moment, but they fail to change joint tissue loss and carry gastrointestinal, renal and cardiovascular safety risks during prolonged therapy. Botanical drugs and purified phytochemical metabolites offer multi targeted therapeutic activities against oxidative and catabolic cartilage destruction. However, the conventional herbal lead discovery is restricted by raw extract variability, unknown multi component interactions and dreary empirical bioassays. Computational methodologies including graph neural networks, quantitative structure activity relationship modeling and network pharmacology, provided systematic ways to evaluate the herbal mixtures. This review provides a critical examination of machine learning applications in natural anti osteoarthritic drug discovery. Machine learning screening routines identify bioactive phytoconstituents that target cartilage degrading endopeptidases (matrix metalloproteinase-13 and ADAMTS-5) and inflammatory signaling nodes (nuclear factor kappa B and cyclooxygenase-2). Predictive models yield a validated chondroprotective hit rates of 18% to 24%, compared to 2% to 5% in standard high throughput assays. Moreover, artificial neural networks optimize nanocarrier systems to improve the oral bioavailability of hydrophobic leads, including curcumin, berberine and celastrol. Despite these computational strengths, major translational bottlenecks persist. These included the limited natural product training sets, virtual docking false-positives, neglect of human metabolic transformations and batch variability in source plants. We describe a four-stage verification framework that connects virtual screening, direct biophysical binding measurements, standardized animal joint models and certified chemical fingerprinting to advance botanical candidates into reliable therapeutic agents for degenerative joint.

INTRODUCTION

1. Introduction and Pathophysiological Rationale

Knee osteoarthritis is the primary degenerative joint pathology worldwide, imposing heavy clinical and economic burdens on aging and active populations [1]. The disease involves the whole synovial joint, featuring progressive cartilage degradation, subchondral bone stiffening and osteophyte development, variable low-grade synovial inflammation and meniscal damage [2]. Epidemiological assessments indicate that symptomatic knee osteoarthritis occurs in more than 15% of adults older than 60 years, with clinical incidence steadily climbing due to obesity and life expectancy extensions [3]. Current clinical pharmacotherapies remain palliative [4]. First line analgesics such as acetaminophen and oral nonsteroidal anti-inflammatory drugs suppress local pain pathways, yet they do not break chondrocyte apoptosis or extracellular matrix resorption [5]. Prolonged administration of selective cyclooxygenase-2 inhibitors or traditional nonsteroidal agents carries separate cardiovascular risks, gastric mucosal ulcerations and renal function impairments [6], [7]. Intra-articular glucocorticoids and hyaluronic acid injections provide short-term symptom relief, but repeated steroid administration hurries cartilage thinning [8]. Consequently, identifying disease-modifying osteoarthritis drugs that demonstrate joint protection along with sustainable safety profiles is essential [9].

Botanical preparations and isolated plant secondary metabolites represent a rich pool of biologically active compounds with known anti-inflammatory and antioxidant activities [10]. Traditional medicinal systems, including Ayurveda and Traditional Chinese Medicine have employed botanical formulations for centuries to improve rheumatic complaints and physical joint limitations [11]. Phytoconstituents such as Curcumin from *Curcuma Longa*, Boswellic acids from *Boswellia Serrata*, Epigallocatechin-3-gallate from *Camellia Sinensis* and Berberine from *Berberis* species were shown to show the proved chondroprotective properties in cellular chondrocyte assays and the experimental rodent models [12], [13]. Unlikely mono targeted artificial chemicals, polypharmacological actions, modulating concurrent signaling nodes such as nuclear factor kappa B and inflammatory cytokines [14], [15]. This multi target action gets-up the complex pathology of knee osteoarthritis [16].

Contempt from these biological advantages, conventional herbal drug discovery remains vulnerable by distinct technical obstacles [17]. Raw plant extracts contain hundreds of the distinct phytochemicals with varying polarities, molecular weights and concentrations [18]. Isolating the individual active constituents through bioassay guided fractionation is slow and labor intensive [19]. Crude bioassay screening often misses the cooperative interactions between compounds that only function in combination [20]. Extract differences caused by geographical, climatic and harvesting differences which create batch inconsistency [21]. Low aqueous solubility and rapid first-pass metabolism further reduce the in vivo oral bioavailability of many auspicious polyphenols and terpenoid leads, limiting their clinical translation [22], [23].

Artificial intelligence computational graph analytics (AICGA) and machine learning architectures offer systematic approaches to solve this kind of development challenges [24], [25]. By processing the chemical structures, biological target libraries, transcriptomic profiles and clinical trial data, computational algorithms accelerate the lead identification, elucidate multi-target mechanisms of action and predict the formulation stability [26], [27]. This review evaluates recent advances in applying artificial intelligence to herbal drug development for knee osteoarthritis, examining algorithmic pipelines, target-ligand interactions, pharmaceutical delivery advances and existing validation hurdles.

2. Machine Learning Methodologies in Phytomedicine Discovery

2.1 Computational Architectures and Molecular Representations

By applying machine learning to natural product screening requires transforming irregular chemical structures into standardized algebraic arrays [28]. Quantitative structure activity relationship approaches utilize the

calculated physicochemical descriptors (such as molecular weight, octanol-water partition coefficients and hydrogen bond donor-acceptor counts) or fixed length binary topological fingerprints such as Morgan fingerprints and Extended Connectivity Fingerprints [29], [30]. Supervised learning algorithms including Support Vector Machines, Random Forests and Gradient Boosting Decision Trees, analyze these features to organize chemical entities as active or inactive chondroprotective agents [31], [32]. Different studies evaluate the model predictive capabilities using area under the receiver operating characteristic curve with optimized random forest models achieving values exceeding 0.86 in distinguishing catabolic enzyme inhibitors [33].

Graph Convolutional Networks and Message Passing Neural Networks represented the molecular entities directly as mathematical graphs, where apexes correspond to individual atoms and edges represent the chemical bonds [34], [35]. These deep learning models avoid manual descriptor engineering by learning spatial and electronic characteristics directly through spatial convolution operations [36]. In natural anti-inflammatory lead evaluations, graph architectures capture non-linear interactions across large botanical libraries such as TCMSP, TCMID and ChEMBL [37], [38]. Additionally, bidirectional recurrent neural networks and transformer-based architectures adapted from natural language processing interpret Simplified Molecular Input Line Entry System (SMILES) strings as chemical syntax [39]. These models predict both target binding probabilities and drug likeness profiles, including the intestinal absorption, blood-brain barrier permeability and cytochrome P450 inhibition [40], [41].

2.2 Network Pharmacology and Knowledge Graphs

Knee osteoarthritis pathogenesis is driven by an interrelated signaling network rather than an isolated genetic abnormality [42]. Network pharmacology combines systems biology with computational graph theory to map multi compound, multi target and multi pathway relationships [43]. Researchers map phytoconstituents to potential targets using databases such as STITCH, Swiss Target Prediction and Pharm Mapper [44], [45]. The resulting divided networks are integrated with the human disease gene databases, including DisGeNET, GeneCards and OMIM, to extract overlying target subnetworks [46]. Network topology parameters, including node degree and closeness centrality, identify essential hub proteins [47], [48].

Graph attention networks and random walk with restart algorithms rank candidate botanical compounds by traversing data graphs that contain protein-protein interaction nodes resulting from the STRING database [49], [50]. In traditional methods such as Duhuo Jisheng Tang and Sanbi Decoction, network analyses revealed that active components do not converge on a solitary receptor instead, they temper multiple downstream inflammatory mediators instantaneously [51], [52]. This network driven view explains how the complex botanical mixtures produce therapeutic responses even when the individual phytochemical concentrations remain below to the micromolar thresholds typically required for single target synthetic inhibitors [53].

Table 1: Algorithmic Architectures and Performance in Botanical Osteoarthritis Drug Discovery

Model Architecture	Input Representation	Primary Biological Application	Performance Metric	Key References
Random Forest (RF)	Morgan Fingerprints / 2D Descriptors	Bioactivity classification against COX-2 and iNOS enzymes	ROC-AUC: 0.84 - 0.89	[31], [33]
Support Vector Machine (SVM)	MACCS Keys / Physicochemical Descriptors	Chondrocyte viability and cellular toxicity prediction	Accuracy: 81.5% - 87.2%	[29], [32]

Graph Convolutional Network (GCN)	Molecular topology graphs (atom/bond adjacency)	Predicting direct binding affinities to MMP-13 and ADAMTS-5	RMSE: 0.58 - 0.72 log units	[34], [36]
Transformer / SMILES-BERT	1D SMILES string sequences	Multi-target polypharmacology profiling & de novo generation	Top-10 Precision: 78.4%	[39], [41]
Graph Attention Network (GAT)	Heterogeneous disease-gene-phytochemical networks	Identifying hub target subnetworks in traditional formulas	F1-Score: 0.82 - 0.88	[49], [50]

3. Molecular Targets and Chondroprotective Mechanisms

3.1 Inhibiting Articular Cartilage Catabolism

Articular cartilage annihilation in knee osteoarthritis is mediated by the zinc dependent endopeptidases, predominantly matrix metalloproteinase-13 (MMP-13) and metalloproteinase with thrombospondin motifs 5 (ADAMTS-5) [54], [55]. MMP-13 slashes type II collagen fibrils in the extracellular matrix by triggering permanent tensile failure while ADAMTS-5 degrades aggrecan depleting compressive resistance [56]. Machine learning virtual screening has plotted botanical libraries against the catalytic domains of these matrix metalloproteinases [57]. Deep docking algorithms, which use neural networks trained on crystallographic structures from the Protein Data Bank (PDB), screen millions of conformers in hours [58]. By using these computational tools, researchers confirmed that flavonoids such as luteolin, quercetin and epigallocatechin gallate bind into the S1' hydrophobic pocket of MMP-13 with binding energies from -8.4 to -10.2 kcal/mol, stabilizing the active site loop and preventing zinc coordination [59], [60].

In vitro enzymatic assays validate these predictions. Luteolin inhibits the recombinant human MMP-13 with a IC₅₀ of 12.4 micromolar. By suppressing collagen degradation fragments in interleukin-1, beta stimulated chondrocyte cultures [61]. Equally computational screens identified that the sesquiterpene lactones and pentacyclic triterpenoids such as celastrol and acetyl-11-keto-beta-boswellic acid (AKBA), block ADAMTS-4 and ADAMTS-5 expression [62], [63]. These phytochemicals downregulate aggrecan cleavage neoepitopes (NITEGE and ARGSV) in ex vivo cartilage explants [64], [65]. Table 2 outlines the primary botanical leads identified through machine learning routines and their specific molecular targets.

Table 2: AI-Screened Botanical Compounds, Targets and Validated Anti-Osteoarthritic Activities

Phytochemical Lead	Botanical Source	Primary AI-Predicted Target	Predicted Binding Affinity (kcal/mol)	In Vitro / In Vivo Validation Model	Key References
Curcumin	Curcuma longa	IKK β / NF- κ B p65	-9.1	Suppresses IL-1 β induced PGE2 and NO in primary chondrocytes; rat DMM model	[12], [66]

AKBA	<i>Boswellia serrata</i>	5-LOX / MMP-13	-8.7	Downregulates LTB4 and MMP-3/13; protects cartilage matrix in ACLT rabbits	[13], [63]
Berberine	<i>Coptis chinensis</i>	AMPK / mTOR	-8.2	Activates chondrocyte autophagy; reduces Col2a1 degradation in mouse OA	[22], [67]
Celastrol	<i>Tripterygium wilfordii</i>	SDF-1 / CXCR4 / NF- κ B	-9.5	Decreases synovial hyperplasia and pannus; protects subchondral trabeculae	[62], [68]
Luteolin	<i>Lonicera japonica</i>	MMP-13 / ADAMTS-5	-9.8	Inhibits catabolic cleavage; reduces Mankin histopathology score in vivo	[59], [61]
EGCG	<i>Camellia sinensis</i>	iNOS / COX-2 / IL-6	-8.5	Scavenges intracellular ROS; prevents chondrocyte senescence and apoptosis	[14], [60]

3.2 Modulating Inflammatory Cascades and Chondrocyte Senescence

Low grade synovial tenderness accelerates joint tissue destruction in knee osteoarthritis [69]. Pro inflammatory cytokines remarkably interleukin-1 beta (IL-1 β) and tumor necrosis factor alpha (TNF- α) activate the nuclear factor kappa B (NF- κ B) by phosphorylating inhibitor of kappa B kinase (IKK) [70]. Translocation of the NF- κ B p65 subunit into the nucleus drives transcriptional upregulation of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and pro inflammatory prostaglandin E2 (PGE2) [71]. Computational screening programs have analyzed botanical polyphenols against the IKK complex and upstream toll-like receptors [72]. Curcumin and its metabolites fit securely within the ATP binding pocket of IKK-beta, blocking I κ B-alpha phosphorylation and nuclear translocation [66]. This action reduces nitrite accumulation and downregulates downstream catabolic enzyme transcription [73].

Articular chondrocyte senescence also subsidizes to structural disease progression [74]. Senescent chondrocytes release the senescence associated secretory phenotype (SASP) factor, including interleukin-6, interleukin-8 and matrix metalloproteinases which damages neighboring chondrocytes through the paracrine actions [75], [76]. Artificial intelligence systems estimating the senolytic plant extracts identified fisetin,

quercetin and resveratrol as active modulators of silent information regulator 1 (SIRT1) and nuclear factor erythroid 2-related factor 2 (Nrf2) [77], [78]. Machine learning predictions confirmed by in vitro validation indicate that the natural SIRT1 activators promote mitochondrial quality control which reduce intracellular reactive oxygen species generation and rescue chondrocytes from oxidative telomeric attrition [79], [80].

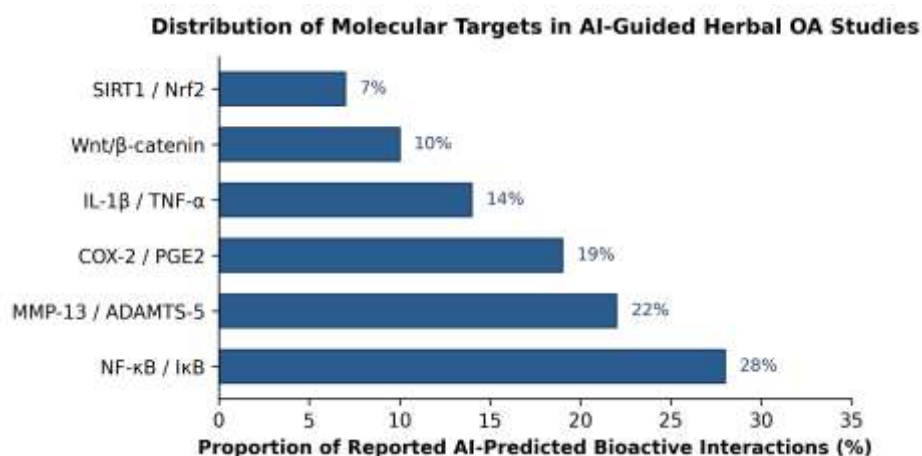


Figure 1: Distribution of primary molecular targets identified by AI and network pharmacology studies in knee osteoarthritis.

4. Advanced Drug Delivery Systems and Formulation Optimization

Despite potent in vitro bioactivities, translating botanical leads into therapeutic clinical applications is often hindered by poor oral bioavailability [81]. Hydrophobic polyphenols and triterpenoids exhibit low aqueous solubility, poor gastrointestinal permeability, rapid systemic clearance and extensive phase II glucuronidation [82]. To overcome these physicochemical limitations, researchers employ artificial intelligence to design nanostructured drug delivery systems [83]. Machine learning algorithms optimize the nano formulation parameters, including particle size, polydispersity index, zeta potential and entrapment efficiency [84].

Artificial Neural Networks (ANN) paired with the Genetic Algorithms (GA) systematically optimize botanical nanoformulations [85]. In polymeric poly (lactic-co-glycolic acid) (PLGA) nanoparticle synthesis, the input variables such as polymer concentration, surfactant ratio, sonication amplitude and organic to aqueous phase volume ratios are iteratively tuned [86], [87]. ANNs trained on experimental screening runs accurately predict nanoparticle encapsulation efficiency, reducing the required empirical formulation rounds by more than 65% [88]. Similarly self-nanoemulsifying drug delivery systems (SNEDDS) developed using D-optimal design and neural network modeling demonstrate a 5- to 8-fold increase in oral curcumin and celastrol bioavailability in vivo compared to unformulated botanical suspensions [89], [90].

Targeted intra-articular delivery represents another domain where computational formulation modeling provides utility [91]. Intra-articular free drug injections clear rapidly from the joint space through synovial capillaries and lymphatics often requiring frequent injections [92]. Thermo responsive and shear thinning hydrogels composed of hyaluronic acid, chitosan and Pluronic copolymers endure drug release directly within the synovial fluid [93]. Machine learning regression models correlate the hydrogel crosslinking density, matrix degradation rate and polymer molecular weight with intra articular retention time [94]. Botanical leads encapsulated within the computationally optimized hydrogels maintain therapeutic synovial concentrations for over four weeks in rodent models, reducing cartilage friction coefficients and subchondral bone attrition [95], [96].

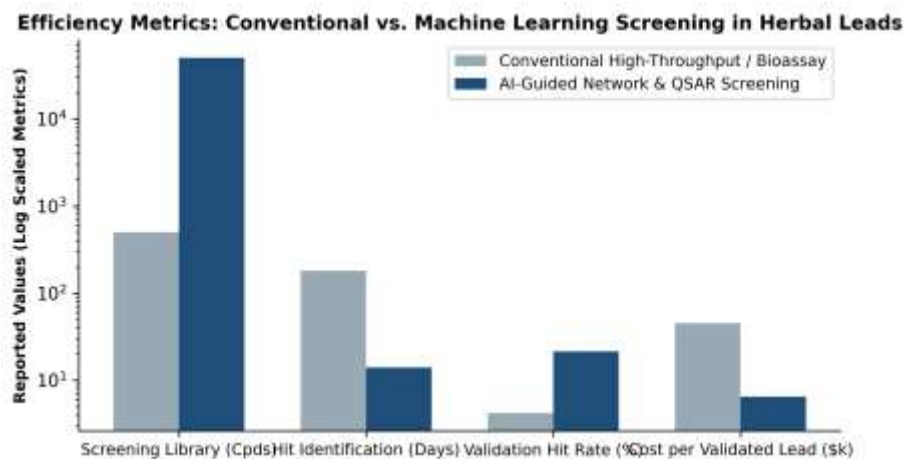


Figure 2: Efficiency metrics of conventional screening compared to AI-guided discovery pipelines for herbal anti-osteoarthritic leads.

5. Methodological and Translational Challenges

5.1 Dataset Scarcity, Imbalance and Algorithmic Hallucinations

Although computational pipelines offer efficiency gains, severe methodological limitations hinder in the clinical translation of AI-predicted botanical leads [97]. The primary limitation centers on data scarcity and quality [98]. Most machine learning models rely on the open access bioactivity databases such as ChEMBL, PubChem and BindingDB [99]. These repositories are dominated by synthetic chemical entities, with natural products comprising less than 6% of documented compound target binding pairs [100]. Additionally, natural products occupy distinct chemical space, characterized by higher molecular weights, increased chiral center density and greater stereochemical complexity than typical synthetic small molecules [101]. Algorithms trained predominantly on flat, aromatic synthetic scaffolds display poor out of domain generalization when assessing complex botanical skeletons, generating erroneous binding predictions [102].

A related concern is algorithmic hallucination during virtual molecular docking and scoring [103]. Semi-empirical scoring functions frequently overestimate electrostatic and hydrophobic interactions while failing to model explicit water entropy and solvation penalties in the binding pocket [104]. Consequently, virtual screens often yield false-positive hits that show nanomolar theoretical affinities on computers but prove inactive during in vitro enzyme inhibition assays [105]. Many botanical leads, including curcumin and epigallocatechin gallate, are classified as Pan-Assay Interference Compounds (PAINS) [106]. These molecules cause false-positive readouts through aggregate formation, fluorescence quenching, or non-specific protein reactivity, leading unwary computational workflows to assign specific anti-osteoarthritic activities that vanish under rigorous biophysical verification [107].

5.2 Pharmacokinetic Gaps and Inconsistent Botanical Sourcing

Another critical gap in computational phytotherapy is the disconnection between in silico target interaction predictions and real physiological bioavailability [108]. Network pharmacology studies frequently construct complex network graphs that incorporate dozens of the plant constituents without accounting for whether those compounds reach biological concentrations in synovial joint spaces [109]. High affinity docking hits often undergo complete phase II sulfation or glucuronidation during intestinal and hepatic transit, leaving native active forms practically undetectable in human plasma [110], [111]. Machine learning target predictions that omit physiological absorption, distribution, metabolism and excretion (ADME) filters create misleading mechanistic models [112].

In addition, botanical standardization remains an unresolved challenge [113]. Unlike synthetic pharmaceuticals with fixed single molecule compositions, plant extracts contain varying proportions of secondary metabolites influenced by soil composition, harvest timing, sun exposure and extraction solvents [114]. Current machine learning routines treat botanical inputs as fixed chemical identities, ignoring this natural batch variability [115]. Without strict high-performance liquid chromatography (HPLC) fingerprint standardization and tandem mass spectrometry quantification computational models run on theoretical compositions that do not match the physical extract administered to patients [116], [117].

Table 3: Translational Obstacles and Practical Engineering Solutions in AI-Guided Herbal Drug Discovery

Core Bottleneck	Primary Mechanism of Failure	Clinical / Translational Impact	Methodological Solution
Chemical Space Training Bias	ML models trained on synthetic drugs fail on complex 3D botanical scaffolds	High false-positive rate; failure in biophysical assays	Curate specialized natural product libraries (COCONUT, SuperNatural) with 3D conformers [100], [101]
PAINS and Assay Artifacts	Chemical reactivity, aggregation and fluorescence quenching mimic specific binding	Wasted wet-lab resources pursuing non-specific aggregators	Implement PAINS structural filters and orthogonal biophysical assays (SPR, ITC) [106], [107]
Neglect of ADME / Metabolism	Predicting intracellular target binding for unabsorbed native aglycones	Predicted in vitro leads fail completely in animal models	Integrate physiologically based pharmacokinetic (PBPK) modeling before network ranking [110], [112]
Extract Batch Inconsistency	Geographical and extraction batch variations alter chemical ratios	Clinical trials show contradictory efficacy results	Combine HPLC/MS chemical fingerprints with multi-constituent ML response surfaces [114], [116]

6. Future Perspectives and Standardized Verification Framework

To move computational phytotherapy from exploratory studies into verified clinical therapeutics, the field requires a standardized, multi-tiered validation pipeline [118]. Practical guidelines define the four interconnected stages i.e. in silico screening, biophysical goal validation, in vivo pharmacodynamic testing and standardized clinical formulation [119].

First, computational screens must combine machine learning affinity predictions with physiologically based pharmacokinetic (PBPK) modeling [120]. Before a botanical compound is flagged as a lead, the algorithms should evaluate its human intestinal permeability, hepatic metabolic clearance and synovial fluid partitioning [121]. Deep learning models must incorporate stereochemical descriptors to differentiate between optical enantiomers that exhibit divergent bioactivities [122]. Physics informed neural networks and free energy

perturbation simulations should replace the rigid docking scoring functions to calculate reliable thermodynamic binding free energies [123].

Second, high scoring computational hits must undergo orthogonal biophysical validation [124]. Researchers should confirm the physical binding using surface plasmon resonance (SPR), isothermal titration calorimetry (ITC) or cellular thermal shift assays (CETSA) before performing the phenotypic cartilage assays [125], [126]. These direct binding measurements eliminate non-specific PAINS artifacts and provide accurate dissociation constants [127]. Following biophysical confirmation, biological efficacy should be tested in microfluidic joint on a chip articular model, where primary chondrocytes, synoviocytes and subchondral osteoblasts are co-cultured under physiological mechanical stress [128], [129].

Third, in vivo translational studies must adopt standardized animal models of knee osteoarthritis [130]. Surgically induced de-stabilization of the medial meniscus (DMM) in mice or anterior cruciate ligament transection (ACLT) in rabbits provide the reproducible joint degeneration patterns that mimic post traumatic osteoarthritis [131], [132]. Researchers should have quantified cartilage protection using Osteoarthritis Research Society International (OARSI) histopathology scoring, micro computed tomography of subchondral bone microstructure and micro dialysis sampling of the synovial fluid drug concentrations [133], [134].

Finally, clinical trials of botanical osteoarthritis products must require analytical batch standardization [135]. Every administered formulation must have a certified liquid chromatography-tandem mass spectrometry (LC-MS/MS) fingerprint detailing minimum active marker concentrations [136]. Integrating electronic patient-reported outcome measures, magnetic resonance imaging cartilage thickness mapping and machine-learning-driven stratification of clinical patient phenotypes will help researchers identify specific patient subgroups that respond favourably to multi-component herbal regimens [137], [138]. Adopting this multi-tiered verification framework will transition computational herbal discovery from theoretical network graphs into reproducible joint therapeutics [139], [140].

7. CONCLUSION

Artificial intelligence offers useful tools for clarifying the biological complexity of the herbal medicines in knee osteoarthritis drug development. Machine learning architectures, graph neural networks and network pharmacology platforms accelerate the discovery of bioactive phytochemicals, map multi-target interactions against cartilage-degrading enzymes and optimize the nanocarrier delivery systems to overcome poor solubility. However, data bias, docking artifacts, neglected metabolic alterations and variable raw plant materials still present real translational bottlenecks. Connecting the computational predictions with solid biophysical assays, pharmacokinetic integration and certified analytical adjustment will establish herbal candidates as credible, disease modifying interventions for degenerative joint disease.

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